adequately taught what others besides those recited in claim 3 possess bioadhesive properties and could be used in practicing this invention". Applicant respectfully traverses the rejection.

Applicant disagrees with the Examiner that the Applicant has not adequately taught bioadhesive microspheres suitable for use in the present invention other than those recited in claim 3. Materials comprising the microspheres suitable for use in the present invention are clearly described in the specification in the second full paragraph on page 5. Additionally, the specification very specifically teaches the preparation of some of the more preferred microspheres to be used in the present invention, namely, starch, albumin, and hyaluronic acid microspheres. In these working examples, found on pages 7-10 of the specification, the components constituting the microspheres and their proportions are recited.

Under the case law, the present language of claim 1 is definite enough to allow one of ordinary skill in the art to determine the scope of that which the applicant regards as her invention. It should be noted that in order to furnish support for claim language, the specification need only mention representative compounds in support of the generic language. In this regard, the Examiner's attention is directed to In re Robins, 166 USPQ 556 (CCPA 1970), which reads in part as follows:

> Mention of representative compounds encompassed by generic claim language clearly is not required by §112 or any other provision of the statute. But, where no explicit description is to be found in the specification (which is not

> the case here) mention of representative compounds may provide an implicit description upon which to base generic claim language. Similarly, representative examples are not required by the statute and are not an end in themselves. Rather, they are a means by which certain requirements of the statute may be satisfied. Thus, inclusion of a number of representative examples in a specification is one way of demonstrating the operability of a broad chemical invention and hence, establishing that the utility requirement of §101 has been met. It also is one way of teaching how to make and/or how to use the claimed invention, thus satisfying that aspect of §112. (166 USPQ at 555) [emphasis added].

Applicant has listed, at page 5 of her specification, many microspheres representative of those suitable for use in her claimed invention. Moreover, by means of several working examples on pages 7-10 and pages 18-26, the Applicant has specifically taught how to prepare and use the microspheres according to the invention. Certainly, the present specification satisfies the requirements of the first paragraph of 35 USC 112 as set forth in the Robins opinion noted above. In this connection, the Examiner's attention is also directed to In re Castaing, 166 USPQ 550 (CCPA 1970) which held that an applicant is entitled to be his own lexicographer.

Furthermore, as one district court noted:

> While it is axiomatic that claims must be interpreted in light of the specification, it is equally well settled that limitations or embodiments contained in the specification generally will not be read into claims. This is in recognition of the basic distinction between claims and specification: "[s]pecifications teach. Claims claim."...if everything contained in the specification were required to be read into the claims there would

> be no need for claims. Nor could an applicant claim more broadly than the particular embodiment or limitation set forth in the specification. In short, it is the claim and not the specification which measures the invention. (citations omitted, emphasis added).

Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1346 (D.Del. 1987), aff'd, 865 F.2d 1247 (Fed. Cir. 1989).

Accordingly, from the evidence and case law herein presented, one skilled in the art would be able to practice Applicant's invention, as now claimed, given the knowledge already possessed in the art at the time of Applicant's filing and the benefit of the teachings of Applicant's specification.

Applicant respectfully requests that the rejection of claims 1-2 and 5-14 under the first paragraph of 35 USC 112, be withdrawn.

Claims 3-4, 6 and 8 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the term 'derivatives' in claim 3 is indefinite; specific derivatives should be recited. Applicant respectfully traverses the rejection.

Numerous starch derivatives suitable for use in the present invention are disclosed in the specification on page 5, last paragraph. Numerous dextran derivatives suitable for use in the present invention are disclosed in the specification on page 6, first paragraph. Additionally, the Examiner's attention is directed to page 5 of the specification, lines 20-23, wherein

Applicant explains that the term "derivatives" is to mean "ester and ethers of the parent compound that can be unfunctionalized or functionalized to contain, for example, ionic groupings".

Given these specific teachings in the specification, it would be well within the ordinary skill in the art to determine, without undue experimentation, which derivatives would be suitable for use in the drug delivery system of the present invention. In fact, it would take no experimentation since specific, suitable derivatives are taught in the specification. To require Applicant to research and define every single starch and dextran derivative capable of functioning in the invention would place an unfair burden on the Applicant, given the vast number of materials suitable for use in the claimed drug delivery composition and disclosed in the present invention. It would be unduly limiting and would risk accidental exclusions. See In re Fretterer, 138 USPQ 217 (CCPA 1963).

In view of the level of skill in the art of those who would be practicing the claimed invention, i.e., biologists, chemists, biochemists, etc., and in view of the teachings of the specification, it would be obvious to one of ordinary skill in the art to determine how to make an embodiment operative, including determining which derivatives would be appropriate. In re Skrivan, 166 USPQ 85 (CCPA 1970). Stated another way, it would be well within the ordinary skill in the art to determine, without undue experimentation, which derivatives were inoperable in the claimed drug delivery system.

As further evidence that starch and dextran derivatives are not indefinite terms, Applicant attaches a dictionary definition of the term "derivative" (Exhibit 8) and also attaches several extracts from standard textbooks wherein starch and dextran derivatives are clearly taught (Exhibits 9-14). In light of the evidence and arguments presented above, Applicant respectfully submits that the language of claims 3-4, 6 and 8 is definite as presently recited. Applicant respectfully requests that this rejection be withdrawn.

Concerning claim 6, the Examiner has inquired whether Applicant intends cross-linking by the expression "stabilized by heat treatment". Cross-linking is not intended by this expression. Heat stabilization is not considered to be clinical cross-linking. Heat stabilization normally denatures the microspheres, specially those made from proteinaceous materials. For microspheres made from other materials such as starch, the heat treatment implements a structural change to the molecule which is not very well defined. Hence, stabilization by chemical cross-linking cannot be considered the same as stabilization by heat treatment.

As described on page 9 of the specification, heat stabilization is presented as one method of modifying a microsphere, for example, when it is desirable to delay the release of the drug from the microsphere.

The Examiner states that the "specific compounds in claim 8 are deemed to be included in 'surfactant' which is also recited".

Applicant has amended claim 8 to delete the redundant language.

Claims 1-5, 11 and 13 stand rejected under 35 USC 102 (e) as being anticipated by Illum (U.S. Patent No. 4,847,091). The Examiner believes the Illum Patent to disclose the same invention. Applicant respectfully traverses the rejection.

U.S. Patent No. 4,847,091 to Illum only discloses compositions comprising sodium cromoglycate. The limitation in claim 1 to systemically active drugs was included specifically to distinguish the claim from this citation. Sodium cromoglycate is not absorbed from the nose into the systemic circulation. Rather, it is used for local treatment, for example when administered nasally for local treatment in the nasal cavity.

In contrast, the composition of the present invention is a delivery system for systemically active drugs. The composition delivers the drug to the nasal mucosa for absorption into the systemic circulation and systemic action. Again, claim 1 of the present invention is limited to a systemically active drug to distinguish it from the Illum Patent teaching only local action.

The specification of the present invention acknowledges that microspheres are known for nasal delivery of systemically active drugs. However, it is specifically taught in the art that such microspheres should be greater than 10μm because smaller particles are thought to escape from the nostrils or migrate into the lungs, and would therefore not be retained in the nasal mucosa. There is thus a prejudice in the art <u>against</u> using microspheres of less than 10μm for nasal delivery of systemically active drugs.

Despite this prejudice, the Applicant experimented with microspheres of less than 10μm. She discovered very surprisingly than not only could microspheres of less than 10μm be successfully used for intranasal delivery of systemically active drugs, but that they provided better absorption and bioavailability of the drugs than the previously used larger microspheres. The data in the specification demonstrates this improved result. There was no way that this improvement could be predicted from the art, which art taught against using microspheres in this small size range. Claim 1 of the present invention specifically limits the size of the microspheres from between 0.1μm to 10μm.

Claims 1-14 stand rejected under 35 USC 103 as being unpatentable over Illum 1986. The Examiner states that "Illum (1986) discloses albumin starch microspheres which could be used to deliver drugs including peptides and proteins to the nasal mucosa. She further discloses that the microspheres could be modified by cross-linking (note the discussion section on page 207). According to Illum such a system would ensure an increased time of contact between the delivery system and the mucosa by a process of bioadhesion with the possibility of additionally releasing the drug from the system in a sustained and controlled manner (note the 3rd paragraph on page 206. The important factors including the particle sizes are also disclosed by Illum (pages 206-207). Pump spray is disclosed on page 208.

Although Illum's teachings do not include the use of penetration enhancers, her disclosure includes the knowledge in the

art of the use of such enhancers for nasal (mucosal) delivery of proteins (see 3rd paragraph, introduction). The instant invention is deemed to be an obvious extension of Illum". Applicant respectfully traverses the rejection.

Illum (1986) discloses the use of microspheres as a system for controlled release of drugs to the nose. While Illum (1986) may discuss the importance of the size of the microspheres for nasal delivery, all of the microspheres disclosed in Illum (1986) are larger than 10μm, with the smallest size disclosed being 20μm. There is no disclosure of using microspheres of less than 20μm for nasal delivery, in accordance with the prevalent prejudice in the art at the time the invention was made. The preferred size range disclosed in Illum (1986) is between 40-60μm. In view of the Illum (1986) disclosure that microsphere size is important, and in view of the sizes disclosed therein, a person skilled in the art consulting Illum (1986) would be taught to use a microsphere size of greater than 10 microns for nasal administration.

Claims 7-12 and 14 stand rejected under 35 USC 103 as being unpatentable over Illum (U.S. Patent No. 4,847,091) or Illum (1986) in view of Hanson et al. or Salzman et al. and vice versa. Specifically, the Examiner states that Illum (4,847,091) does not teach penetration enhancers. Illum (1986) discloses awareness in the art of penetration enhancers but does not use enhancers with the microspheres.

The Examiner further states Hanson et al. disclose that biological response to nasal administration of calcitonin could be

increased by inclusion of various surfactants in the formulations. The Examiner continues that, although the disclosure of Hanson et al. does not include use of microspheres, an artisan could interpret the term "formulations" as inclusive of microspheres.

Concerning Salzman et al., the Examiner states that the reference discloses intranasal administration of insulin in combination with a non-ionic detergent increases the absorption of insulin. The Salzman disclosure, however, does not include microspheres.

The Examiner thus concludes that "[T]o include penetration enhancers such as surfactants taught by Hanson et al. or Salzman et al. in the microspheres of Illum or Suzuki et al. (assuming phospholipids are not penetration enhancers) for nasal delivery for drugs including insulin would have been obvious to one of ordinary skill in the art at the time the invention was made since such an inclusion would certainly increase the absorption of drugs by mucosal membrane.

Alternatively, to use the microspheres of starch or similar swellable and bioadhesive material as taught by Illum (1986) Illum (4,847,091) in the teachings of Hanson et al. or Salzman et al would have been obvious to one of ordinary skill in the art since such spheres adhere to the nasal mucosa and allow the drug to be released in a sustained manner". Applicant respectfully traverses the rejection.

None of the above cited art disclosing microspheres teaches that for intranasal delivery for <u>systemic</u> distribution of

a drug, the microspheres should be of a size from 0.1μm to 10μm.

Illum (4,847,091) does not provide a pharmaceutical composition for systemic distribution of the drug throughout the entire body. It is limited to local action at the site to be treated. Sodium cromoglycate is not absorbed into the systemic circulation. Illum (1986), as noted above, only teaches microspheres of 20μm or larger. Neither Hanson et al. nor Salzman et al. disclose microspheres in the size range required by claim 1 of the present invention. Suzuki et al., mentioned only by the Examiner as an item of interest, teach that the particles of the composition should have a diameter of 10-250μm and specifically teach not to use particles of smaller diameter.

However, even though the prior art taught against using microspheres less than 10μm in size, Applicant experimented with the contraindicated sizes and, unexpectedly, found that the use of microspheres of less than 10μm provided significant improvements over larger sized microspheres. The examples in the specification illustrate these surprising results when microspheres of less than 10μm are used for nasal administration of a drug for systemic distribution.

Example 1 compares the intranasal administration of insulin in sheep with starch microspheres of greater than 10μm and less than 10μm. The results shown in Figure 1 show that a 25% increase in the blood concentration of insulin was obtained using the small (<10μm) starch microspheres compared with the larger starch microspheres. This is a very significant increase and could

not have been predicted.

Example 3 demonstrates that improved intranasal absorption of insulin in sheep was obtained using small (<10μm) hyaluronic acid and hyaluronic acid-dextran microspheres compared with larger microspheres of starch.

Example 2 compares the decomposition of small and large starch microspheres in the human nasal cavity. Figure 2 illustrates that a much longer residence time in the nasal cavity was achieved using microspheres of 1-10μm compared to that with microspheres of 40μm. These results are totally unpredictable and are in direct contradiction with the teachings of the cited art.

Additionally Applicant encloses data, verified by the inventor, using the drug granulocyte-colony stimulating factor, to show that an improved result was obtained with the small microspheres according to the invention as compared with larger microspheres. (Exhibit 15).

In view of the above amendments and remarks, Applicant respectfully submits that the claimed invention is patentably distinguishable over the references of record or any combination thereof. A notice to that effect would be appreciated.

It is believed that there are no fees due with the filing

of these papers. However, in the event fees are due, please charge deposit account No. 12-2147.

Respectfully submitted,

LORUSSO & LOUD

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on this 21st day of March, 1994.

By Patricia Jimenez